



Bristol-Myers Squibb Company

Richard L. Wolgemuth, Ph.D.
Senior Vice President
Global Regulatory Sciences
Pharmaceutical Research Institute

P. O. Box 4000 Princeton, NJ 08543-4000
Tel 609-252-6503 Fax 609-252-7350
Richard.Wolgemuth@bms.com

July 9, 2004

**Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852**

Re: Docket No. 2004D-0189; BMS ID No. 0497. Draft Guidance, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (*Federal Register* May 5, 2004)

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, infant formulas, and nutritional products, is pleased to have the opportunity to offer comments on the Draft Guidance on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. Our comments are set forth below.

Summary of BMS Comments on Proposal

BMS commends the FDA on the development of the guidance document that describes the FDA's philosophy and approach to pharmacovigilance activities, specifically defined as "post-approval risk assessment activities" including "all observational (non-randomized) scientific and data gathering relating to the detection, assessment and understanding of adverse events." We further commend the FDA on their attempts to harmonize this guidance with international definitions and standards.

BMS concurs with the FDA regarding the need for clear and comprehensive guidance on improving the quality of spontaneously reported cases to facilitate good pharmacovigilance, the utility of data-mining using statistical or mathematical tools to complement traditional pharmacovigilance methods, the use of pharmacoepidemiologic and observational studies to evaluate actual risk relative to a potential safety signal, and development of pharmacovigilance plans in instances of unusual safety concerns. However, BMS suggests further clarity and consideration around the process for obtaining permission from consumers to contact health care providers (HCPs) for complete medical information and the process for obtaining information that may not be forthcoming from HCPs regarding medication errors. BMS suggests that while data mining may yield information regarding potential safety signals, it may be premature to suggest that mathematical methods be used to routinely (systematically) identify potential signals. Furthermore, BMS requests that FDA provide further explanation of the circumstances and process under which questions on potential safety risk and pharmacovigilance plans may be brought before its Drug Safety and Risk Management Advisory

2004D-0189

C9

Committee.

Specific Comments (Items that Need Clarification & Recommended Actions)

Targeted queries regarding adverse events (Section IV.A., lines 149-153):

- BMS concurs with the FDA that queries regarding spontaneous case reports be focused on clinically relevant information associated with the product and the adverse event (AE). To facilitate this line of questioning, the FDA suggests that computer assisted interview technology and other methods be employed. BMS recommends the Guidance specifically define “other methods,” such as use of targeted questionnaires regarding AEs of special interest.
- When the report is from a consumer, the consumer must grant the sponsor permission to contact the consumer’s HCP. However, existing HIPAA regulations may preclude effective follow-up from the HCP. BMS recommends the FDA specify if permission must be granted via first verbal and then written contact with the consumer or whether such permission can be obtained via written correspondence alone. Direct verbal contact with the consumer would add an extra step in the process, since written permission would still be required from the consumer.

Intensity and method of case follow-up (Section IV.A., lines 155-159):

The Guidance suggests that the intensity and method of case follow-up be determined by the relative seriousness of the event, the type of reporter, and other factors, with the most aggressive follow-up efforts directed towards serious adverse event reports. BMS recommends that the Guidance include definitions of “intensity and methods of follow-up” and “aggressive follow-up” as follows:

- Aggressive follow-up: telephone contact using a targeted questionnaire, limited to serious unexpected cases reported by HCPs with written confirmation of the telephone contact
- Follow-up for serious expected and non-serious unexpected cases: to be done via letter
- Serious unexpected cases from a consumer: company should seek written authorization from the patient to contact their HCP

Characteristics of a good case report (Section IV.B., lines 161-185):

In general, BMS concurs with the characteristics of a good case report as listed in the draft Guidance. However, BMS requests that the Guidance specify whether all of these elements are required for all adverse events or just serious cases. Furthermore, BMS recommends the Guidance include further clarity/confirmation regarding which reported associated signs and symptoms can be subsumed under a unifying diagnosis if provided by the reporter.

Additional information required for medication error reports (Section IV.B., lines 188-199):

BMS notes that the work environment (line 196) and types of personnel involved (line 198) with a medication error are not under the control of the sponsor, and should not be required elements of a medication error report, particularly as it is probable that institutions involved in medication errors would be reluctant to provide this specific information to a company. Also, BMS suggests noting that if no AE occurred, most of the elements listed for a good case report (lines 165-186) will not apply. Further, BMS suggests that the narrative information is best obtained in a format compatible with MedWatch, rather than that of the NCC MERP Taxonomy referred to in the draft Guidance (line 201).

Developing a case series and assessment of causality (Section IV.C., lines 207-279):

- In order to enhance the utility of AERS in monitoring drug safety, BMS recommends shortening the time interval for public release and strengthening the quality of the information.
- BMS concurs with the FDA's recommendation that sponsors look for features in cases that may suggest a causal relationship when reviewing a case series during signal detection activities. BMS also agrees that sponsors should be more conscientious in gathering additional information when confounding factors are present. However, BMS recommends clarification of the word "causality" in the title in line 207, as it appears that FDA is suggesting that a causality assessment be required for spontaneous case reports. This appears contrary to the discussion that follows regarding the absence of internationally agreed upon standards or criteria for assessing causality in individual cases, and the notion that rigorous pharmacoepidemiologic studies are usually needed to assess causality, particularly for spontaneously occurring events.
- If the safety signal relates to a medication error, BMS concurs with the FDA that it is good public health policy to report root causes. However, BMS recommends that the FDA reflect in this Guidance that a sponsor faces significant barriers beyond a sponsor's control in obtaining such information and that the sponsor must rely on the U.S. reporter for obtaining these facts. As a result, it is unlikely that sponsors will be able to obtain such information. Further, dispensing and administrative process failures for medication errors are similarly difficult for sponsors to investigate and report and the FDA should reflect these difficulties by adjusting the requirements for mandatory good reporting practice in this Guidance appropriately..

Summary descriptive analysis of a case series (Section IV.D., lines 281-307):

- In the event one or more cases suggesting a safety signal warrants additional investigation, BMS concurs with the FDA in the assembly and summarization of a case series.
- Given that lot numbers are generally not provided or available when adverse events are reported, BMS recommends adding the wording "if available" in line 304 (...lots, if available..).

Data mining (Section IV.E., lines 309-353):

- Although BMS appreciates FDA's interest in including a section on data mining in the Guidance, given that these techniques are generally considered exploratory, with no consistent standards, and are not routinely applied and evaluated, BMS suggests caution in interpreting findings or making conclusions based on such techniques. It is premature to suggest that data mining be used routinely (systematically) to identify potential signals. There are substantial potential limitations and liabilities if these tools are not used correctly. For example, false positives may be incorrectly identified, potentially leading to misplaced legal liability. It should be clarified that these statistical tools are not a substitute for traditional medical review of aggregate data, and should be used in conjunction with traditional methods for signal detection and not as a replacement. With all these caveats, it may be premature to include this section in the Guidance.
- FDA should clarify under what circumstances, if any, it would be appropriate to request results of a sponsor's own exploratory data mining activities. Furthermore, if the FDA conducts its own data mining activities, it should be specified when and in what format results will be provided to the sponsor.
- Lines 326-327 suggest that there is a standard procedure to determine optimum thresholds, sensitivity and specificity. BMS suggests the text be modified to indicate that data mining

methods have not been systematically validated, and there is a great deal of uncertainty about their predictive value, sensitivity and specificity.

- In line 329, BMS suggests adding the word “potential” to the phrase, “It is not unusual for a product to have several “potential” signals identified...”
- Regarding use of AERS (lines 340-342), BMS recommends adding co-morbid illness and numerous potential unmeasured/unrecorded confounders as inherent biases of AERS.

Safety signals that may warrant further investigation (Section IV.F., lines 355- 384):

Although BMS agrees that in evaluating potential safety signals, the actual risk to patients may be greater than the estimated reporting rate due to under-reporting, there are circumstances of stimulated reporting in association with a competitive commercial environment or lay/scientific media attention (as alluded to in line 441) that need to be considered.

Calculating reporting rates vs. incidence rates (Section IV.G., lines 386-445):

- BMS recommends the FDA elaborate further regarding the limitations of comparing reporting rates (line 420). For example, a comparator drug may have entered the market at a different time under more competitive marketing conditions or under a very different level of safety scrutiny, resulting in significant differences in the reporting rates during given post-launch time intervals.
- BMS would appreciate more information on the FDA’s estimate of under-reporting for unstimulated reports (line 436). Does the FDA concur with the often quoted 10% of events actually being reported relative to those that likely have occurred in the population?

Beyond case review: investigating a signal through observational studies (Section V):

BMS commends the FDA on incorporating into this section industry recommendations regarding the previously published Concept Papers.

Interpreting safety signals: From signal to potential safety risk (Section VI., lines 633-697):

Overall, BMS agrees with FDA regarding sponsor case level review, assessing product relatedness, and descriptive summarization of case series. BMS recommends the FDA further define the threshold at which an identified safety signal represents a potential safety risk triggering a formal submission (line 645). Currently, the addition of postmarketing adverse events to labeling occurs through routine pharmacovigilance and periodic reporting practices. This section appears to apply to serious, unexpected safety risks that significantly impact the benefit-risk balance, but this is not clearly stated. Regarding assessment of benefit-risk balance (line 666), BMS recommends FDA provide further guidance on how this balance is to be quantified or established, or refer the reader to one of the other Guidance documents..

Developing a Pharmacovigilance Plan (Section VII, lines 699-782):

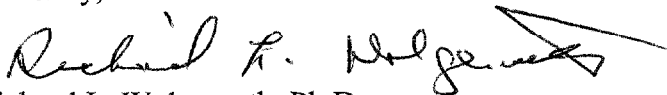
- Overall, BMS concurs with the FDA description of pharmacovigilance plans. However, a pharmacovigilance plan describes plans for risk assessment above and beyond routine postmarketing reporting efforts (e.g. enhanced expedited and periodic reporting and/or pharmacoepidemiologic studies) and does not in and of itself provide for risk minimization. Thus, BMS recommends that a pharmacovigilance plan should be viewed as an informative element of a Risk Minimization Action Plan (RiskMAP), and supplementary to a RiskMAP as an element of an overarching Risk Management Plan.
- BMS recommends the FDA provide its view on examples of significant safety issues which

arose post-approval as provided in the CIOMS V report as well as its assessment of situations where at-risk populations were not adequately studied pre-marketing, or when a rare, serious event requiring active surveillance would be justified (degree of corresponding benefit necessary to make this risk acceptable). BMS further requests that FDA provide its view on whether active surveillance is envisioned for 1) products that do not have signals but on theoretical grounds may pose such risks, 2) when a signal has arisen but it has not been fully assessed in terms of causality, and 3) when a serious event is too infrequent to assess through randomized, controlled trials in several thousand exposures.

- BMS recommends that FDA provide further explanation of the circumstances under which FDA may bring questions on potential safety risk and pharmacovigilance plans before its Drug Safety and Risk Management Advisory Committee. Included in this description should be more specific guidance around sponsor notification and communication to assure that the development of the pharmacovigilance plan and/or RiskMAP and preparation for the advisory committee evolve as a partnership between FDA and the sponsor.

BMS appreciates the opportunity to provide comment and respectfully requests that the FDA give consideration to our recommendations. BMS would be pleased to provide additional pertinent information as may be requested.

Sincerely,

A handwritten signature in black ink, appearing to read "Richard L. Wolgemuth", with a stylized flourish at the end.

Richard L. Wolgemuth, Ph.D.
Senior Vice President,
Global Regulatory Sciences